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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,462	09/18/2001	Jeffrey Wilusz	601-1-109N	7730

34055 7590 08/11/2003

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EXAMINER	
LAMBERTSON, DAVID A	

ART UNIT	PAPER NUMBER
1636	21

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,462	WILUSZ ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,9-17,19,20 and 22-40* is/are pending in the application.

4a) Of the above claim(s) *14-16 and 22-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,9-13,17,19,20 and 27-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 May 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt is acknowledged of a reply, filed May 23, 2003 as Paper No. 17, to the previous Office Action. Amendments were made to the claims. Specifically, claims 4, 7, 8, 18 and 21 are cancelled, and new claims 27-40 are added.

It is noted that applicant has inexplicably replaced pending claims 22-26 with new claims 22-35. The claims have been renumbered according to 37 CFR 1.126 to represent newly added claims 27-40, instead of claims 22-35 as listed in the original amendment. The newly added claims will be referred as they are renumbered in the ensuing Office Action, unless otherwise indicated.

Although the amendment is technically not in compliance with either the new or old rules for making an amendment (the replaced claims are not properly annotated as withdrawn), the examiner has provided an Office Action on the merits in the interest of compact prosecution. Applicant is reminded that in order for an amendment to be in compliance with the new rules (implemented in force as of July 30, 2003), all of the pending claims must be present in the application, including those that are withdrawn or cancelled.

Claims 1-3, 5, 6, 9-17, 19, 20 and 22-40 are pending in the instant application. Claims 14-16 and 22-26 are withdrawn from consideration. Claims 1-3, 5, 6, 9-13, 19, 20 and 27-40 are ready for examination in the instant application. Any rejection of record in the previous Office Action, mailed December 17, 2002 as Paper No. 15, that is not addressed in this action has been withdrawn.

Because this action either maintains rejections set forth in the previous Office Action or raises new grounds of rejections that are necessitated by amendment to the claims, this Office Action is made FINAL.

Information Disclosure Statement

The information disclosure statement filed May 28, 2003 as Paper No. 20 has been considered, and a signed and initialed copy of the form PTO-1449 has been attached to this Office Action.

Drawings

New corrected drawings are required in this application because of the reasons set forth on the second Draftsperson's review form (PTO-948). Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Oath/Declaration

Applicant's new Declaration has been entered into the specification.

Response to Amendment

It is acknowledged that applicant has invoked 35 USC§ 112, Sixth Paragraph practice as it regards claims 27, 28, 30, 33 and 37-40 (formerly claims 22, 23, 25, 28 and 32-35). It is noted that applicant originally indicated that former claims 22, 23, 25, 27, 29, 33 and 35 were "means-plus-function" claims. However, several of these claims did not contain "means-plus-function" language (former claims 27 and 29), while other non-indicated claims did contain "means-plus-function" language (former claims 28, 32 and 34). In order to make the record clear, the examiner has properly indicated the "means-plus-function" claims as former claims 22, 23, 25, 28 and 32-35. As indicated above, these claims have also been renumbered according to 37 CFR 1.126 as claims 27, 28, 30, 33 and 37-40. Applicant is reminded that by invoking 35 USC 112, Sixth Paragraph they are limited to the means specified in the written description of the instant specification. Since applicant has met the three-prong analysis for invocation of 35 USC 112, Sixth Paragraph, these claims are being treated under 35 USC 112, Sixth Paragraph.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 6, 9-13, 27-31 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. Specifically, there is no support in the specification for the term "substantially free of polysomes". Applicant indicates in their response that support for this amendment is present on page 15, lines 6-9; however, the term "substantially free of polysomes" does not appear there, or at any other location in the specification. This is a new matter rejection. **This is a new rejection that is necessitated by amendment.**

Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection that is necessitated by amendments to the claims.**

Specifically, the claim relies on the invocation by applicant of 35 USC 112, sixth paragraph, regarding means-plus-function claim limitations; 35 USC 112, sixth paragraph requires that applicant be limited to the means specified in the written description. The claim recites a "means for sequestering proteins that bind to poly(A)" limitation, where applicant points to another specification (US Application No. 09/320609) for support of this amendment. This is an improper incorporation by reference because applicant has not clearly defined the means specified in the claims in the instant specification, which is an element that is essential to the claimed invention.

Claims 1-3, 6, 9-13, 17, 19, 20 and 27-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an S100 HeLa cell cytoplasmic

extract, does not reasonably provide enablement for all mammalian cell extracts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This rejection is maintained for reasons set forth in the previous Office Action, and is now applied to new claims 27-40.**

It is noted that the rejection of claims 4, 5, 7, 8 and 21 have been withdrawn in view of amendments to the claims. The application of the rejection to newly added claims 27-40 is based on their dependence on a claim that is rejected under 35 USC § 112, first paragraph, wherein the depending claims do not ameliorate the scope of enablement issues concerning the independent claim.

Response to Arguments Concerning Claim Rejections - 35 USC § 112, First Paragraph

Applicant's arguments filed May 23, 2003 have been fully considered but they are not persuasive. Applicant's arguments are as follows:

1. Undue experimentation is not required to practice the invention because the disclosure provides considerable direction and guidance on how to practice the invention and presents working examples, and all of the required methods are known in the art. Thus the examiner's contention of undue experimentation appears to be defined only in terms of the number of experiments required to practice the full scope of the claims.

2. If the skilled artisan were to follow the procedures set forth in the instant specification by applicant (e.g., making the same type of cell extract, adding a methylated cap analog to determine if a decapping activity was present, etc.), they would be able to determine if any other

mammalian cell extract contained decapping activity. Thus the experimentation is routine, and HeLa cell cytoplasmic extracts are a representative working example of all other cell types.

3. That because there was no direct evidence in the past for decapping of mRNA in mammalian cells does not indicate that the level of skill in the art was underdeveloped; rather it indicates that it was merely unrecognized and unappreciated.

4. That the art of measuring decapping of mRNA in yeast indicates that a method of decapping mRNA in mammalian cells is well developed.

5. That in contrast to the examiner's assertion that working examples are not presented for non-HeLa cell types, the specification provides sufficient guidance for other mammalian cells because the HeLa cell extract is representative of all other mammalian cell types.

6. That the art is not unpredictable because nobody had previously been able to show decapping of mRNA in mammalian cells; rather, it was simply unrecognized and unappreciated in the art, and in light of applicant's teachings, one would appreciate that decapping of mRNA in mammalian cells would occur in exactly the same manner as it does in other types of mammalian cells.

In response to applicant's arguments, the examiner makes the following points:

1. The number of experiments is not the only factor that has been considered with regard to the scope of enablement rejection presented in the previous Office Action. Instead, it is the unpredictability of the art that has been embraced by the instant specification (that there has been no direct biochemical evidence for mRNA decapping in mammalian cells) that gives rise to the non-enablement of the full scope of the invention. The examiner recognizes that the applicant has provided useful information regarding decapping in HeLa cells, but they have provided

working examples and guidance with regard to those cells alone. Importantly, it is an unexpected result, the addition of methylated cap analogs to the cell extract, which has led to the discovery of decapping in HeLa cells. Because this result is unexpected, and was not required for measuring decapping in other eukaryotic cells (see the review provided for mRNA decapping in yeast cells), the skilled artisan could not reasonably expect that this same procedure would necessarily work in all other mammalian cells, thus the experimentation involved requires undue *and unpredictable* trial and error experimentation.

2. Again, the examiner acknowledges the fact that the instant specification provides working examples and guidance with respect to the use of HeLa cells. However, the examiner also points out that the level of skill in the art and the state of the art indicate a high level of unpredictability in the art. While the skilled artisan would certainly be able to perform the biochemical steps involved in the mRNA decapping protocol set forth in the instant specification, there is no reason to expect that the decapping activity would be in any particular cellular extract at a detectable level or that the addition of methylated cap analogs would necessarily result in the detection of capping activity. This is supported by the fact that mRNA decapping in yeast cells, to which applicant later draws an analogy in their arguments, does not require the addition of a cap analog in order to detect the decapping activity. Rather, this is an unexpected result that pertains to HeLa cells, which raises the question as to whether this or some other step would be necessary in the context of other mammalian cell types, which encompass a great number of distinct species and corresponding cell types.

3. Simply substituting the words "unrecognized and unappreciated" for the word "underdeveloped" does not make the level of skill in the art any more developed. If the

decapping process in mammalian cells was not previously known to occur, i.e., unrecognized, then it would be impossible for the skilled artisan to have a high level of skill in the art. As such, an "unrecognized and unappreciated" field is equivalent to the skill in the art being underdeveloped, absent some teaching that the skill in the art was well developed.

4. The state of the art of mRNA decapping in yeast is virtually irrelevant to the state of the art as it regards decapping in mammalian cells for at least two reasons. First, yeast is not a model system for all mammalian cells despite the fact that it is a eukaryotic cell, thus the predictability in the art of mRNA decapping in yeast does not correlate to predictability in the art of mRNA decapping in mammalian cells. This is further supported by the second fact, which is that unlike HeLa cells (as an example of a mammalian extract), yeast cells do not require the addition of a methylated cap analog to stimulate decapping. Because yeast cells do not require a step that is vital to the process for measuring decapping in HeLa cells, as taught by the instant specification, one cannot establish a reasonable expectation of success when using all types of mammalian cells on the state of the art as it regards yeast cells.

5 and 6. As stated previously, the recitation of a single example is not a reasonable representation of working examples for all types of cells. Mammalian cells comprise a vast number of organisms and a corresponding number of cell types. Applicant's results regarding the detection of mRNA decapping in HeLa cells involve an unexpected, unpredictable step (the addition of a methylated cap analog) that is not required in other mRNA decapping systems. In light of the level of skill in the art, the state of the art, and the unpredictability of the art, a single working example of a mammalian cell is not predictive of what would happen in all other mammalian cells.

In conclusion, the examiner maintains the scope of enablement rejection based upon the following facts: Applicant's results are based on an unexpected result, the addition of a methylated cap analog to stimulate mRNA decapping in mammalian cells, as this is not required for other mRNA decapping systems, such as yeast. In light of this unexpected result and its relationship to the yeast system (which applicant considers a reasonable representation of the state of the art), the full scope of the invention is unpredictable because the vital step for the instant invention is not required for the reasonable representation of the state of the art. Furthermore, applicant acknowledges that the level of skill in the art was previously "unrecognized and unappreciated" which is equivalent to the level of skill in the art being underdeveloped. Given a single working example of mRNA decapping in a single cell type, and in view of the state, unpredictability and level of skill in the art, the skilled artisan would be required to practice undue and unpredictable trial and error experimentation.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5, 6, 9-13, 27-31, 38 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections necessitated by amendment of the claims.**

Claims 1 and 39 recite the limitation "substantially free of polysomes." "Substantially free" is not defined in the specification, thus it is unclear what is meant by "substantially free".

Furthermore, "substantially free" is a relative term that in the absence of a clear definition renders the metes and bounds of the claim indefinite.

Claims 31 and 38 recite the acronym "ARE" without first defining the acronym. It is appropriate to define an acronym upon its first appearance in the claims. Since the term is not defined in the claim, the term is indefinite. It would be remedial to indicate that an ARE is an AU-rich element.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Prior to rejection of the claims, it is important to note that the claims are drawn to a kit comprising several elements as a composition. The recitation of a kit in the preamble of the claims is interpreted as an intended use, and does not carry patentable weight beyond that of the composition as contained within the kit. It is also important to note that applicants definition of "cap-labeled" encompasses any capped mRNA substrate that can be measured, including a radioactive or non-radioactive isotopic label, or any other detectable group which does not interfere with the decapping system (see for example page 15, lines 19-28).

Claims 17, 20, 35 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Hellmann *et al.* (*J. Biol. Chem.* **257**(8): 4056-4062, 1982; see entire document; henceforth Hellmann). **This is a new rejection necessitated by amendment to the claims.**

Hellmann teaches a cytoplasmic reticulocyte cell extract containing a capped mRNA and a methylated cap analog (see for example the Abstract). Hellmann teaches the use of a rabbit reticulocyte lysate (a mammalian cell cytoplasmic extract) to detect the presence of a cap-binding protein. Hellmann teaches the preparation of 7-methyl GTP cap-labeled mRNA (e.g., m^7Gppp(Np)G(^{32}P)Cp) (see for example page 4057, paragraph bridging the left and right columns) and its ability to bind to the cap binding protein of rabbit reticulocyte lysates (see for example page 4059, bridging paragraph for the left and right columns, to page 4060, bridging paragraph between pages 4059-4060). This mRNA substrate qualifies as a cap-labeled mRNA substrate because it can be recognized by antibodies to the methylated cap (7-methyl GTP) of the mRNA. The antibodies were well known in the art at the time of the invention, thus the mRNA substrate taught by Hellmann meets the definition of "cap-labeled mRNA substrate" as set forth in the instant specification. This is because the cap of the mRNA serves as the visibly detectable moiety in the presence of antibodies, using a visible detection system such as a western blot. Hellmann also teaches using the cap analog 7-methyl GTP (see for example page 4057, left side, first paragraph) in the reticulocyte lysate fraction to inhibit binding of the cap-labeled mRNA substrate (see for example page 4059, second paragraph, right column). Since the cap-labeled mRNA is made of RNA, it necessarily contains an "RNA element". Furthermore, Hellmann anticipates the "means for decapping a cap-labeled mRNA substrate" limitation under 35 USC 112, Sixth Paragraph because the "means" described in the instant specification is a cap analog

(see for example page 31, lines 23-24), which is taught by Hellmann as set forth above concerning the 7-methyl GTP cap analog. Thus, Hellmann teaches the composition set forth in the kit as claimed in the aforementioned claims (i.e., a mammalian cell extract, a methylated cap analog [a.k.a., a means for decapping a cap-labeled mRNA substrate], and a cap-labeled mRNA substrate having a visibly-detectable moiety and an RNA element), and therefore anticipates the claimed invention because a kit is an intended use.

Response to Rejections Concerning Claim Rejections - 35 USC § 102

Although the rejections are necessitated by amendment, applicant's arguments concerning the previous rejections are relevant to the instant rejections, and are discussed for the benefit of applicant's understanding of the current rejection.

Applicant's arguments are as follows:

1. Hellmann does not teach the absence of polysomes.
2. Hellmann does not teach a cap-labeled mRNA substrate.

Applicant's arguments are not convincing for the following reasons:

1. The claims that are instantly rejected do not contain a limitation concerning the absence or presence of polysomes, therefore the argument is irrelevant to these claims.

2. Hellmann does in fact teach a cap-labeled mRNA substrate. Applicant's definition of a "cap-labeled mRNA substrate" is set forth on page 15, lines 19-28 of the instant specification. By this definition, any structure on a cap-labeled mRNA that gives a detectable signal reads on a cap-labeled mRNA substrate. Antibodies for the 7-methyl GTP cap of an mRNA were well known in the art at the time of the invention (see for example Rainen *et al.*, *Nuc. Acids. Res.* **12**: 3877-

3889; see the Abstract, which is provided for applicant's reference). It is well known in the art that antibodies give a visibly detectable signal in such methods as alkaline-phosphatase or horseradish peroxidase based western blot analysis, both of which are conveniently included as a means for visible detection of the cap-labeled mRNA substrate (see for example page 26, lines 10-16). Therefore, the recognition of a capped mRNA substrate using an antibody would constitute that the mRNA was cap-labeled, by applicant's own definition. Thus any mRNA having a 7-methyl GTP cap is indeed a cap-labeled mRNA substrate. It is important to note that the Rainen reference is supplied not as a necessary part of the composition, but simply to support that the teachings of Hellmann are not deficient in the area of a cap-labeled mRNA substrate because the cap itself is a detectable moiety, and is thus labeled. Since the antibody does not impart any necessary element of the composition (e.g., it is not a part of the cap-labeled mRNA substrate, per se), it is not required for the rejection by Hellmann.

Allowable Subject Matter

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
August 8, 2003

DAVID GUZO
PRIMARY EXAMINER